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ADDENDUM FOR FLUORANTHENE

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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information form Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Fluoranthene.

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CHO	Chinese hamster ovary
CRAVE	Carcinogen Risk Assessment Verification Endeavor
DNA	Deoxyribonucleic acid
HGPRT	Hypoxanthineguanine phosphoribosyl transferase
K_{oc}	Water/octanol partition coefficient
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
RfD	Reference dose
RQ	Reportable quantity

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$\text{RfD} = \frac{\text{NOAEL or LOAEL}}{\text{UF(s)} \times \text{UF}}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multi-stage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on fluoranthene, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

Recent data are available regarding the oral toxicity of fluoranthene (U.S. EPA, 1988). In a 13 week study male and female CD-1 mice (20/sex/group) were administered 0, 125, 250 or 500 mg/kg/day of fluoranthene dissolved in corn oil. Baseline blood evaluations were determined during the first week of the study, from an additional 30 animals/sex/group. Body weights, food consumption and clinical signs of toxicity were monitored at regular intervals during the experimental period. At the end of the study period the animals were sacrificed, autopsy; hematologic and serum chemistry evaluations were also performed.

Treated mice exhibited increases salivation (never exceeding 10% of the population of any treatment group), and dose dependent increases in pigment accumulation in the liver and mild nephropathy characterized by the presence of multiple foci of tubular regeneration. A small, but statistically significant, increase in relative liver weight was observed in mice receiving 125 mg/kg/day of fluoranthene. Statstically significant changes in mice receiving 250 mg/kg/day included increases in SGPT and absoulte and relative liver weights, as well as decreases in packed cell volume and red blood cell numbers (females only) and A/G ratios. Statistically significant observations in mice receiving 500 mg/kg/day included increases in SGPT, serum globulin and absolute and relative liver weights, as well as decreases in packed cell volume (females only and A/G ratios. Based on the lack of dose related increase in clincal signs and lack of adverse kidney and liver

histopathologic changes the 125 mg/kg/day dose was considered a NOAEL (U.S. EPA, 1990). Based on hematologic alterations, increased SGPT levels, and changes in kidney and liver histopathology in animals receiving 250 mg/kg/day, this dose level was considered as the LOAEL.

The U.S. EPA (1980) had concluded that fluoranthene is not a carcinogen, cancer initiator or promoter, or mutagen; however, more recent evidence by Busby et al. (1984) suggests that fluoranthene may be a complete carcinogen. Newborn male and female mice of Swiss-Webster BLU:Ha strain were injected intraperitoneally with a total dose of 700 µg (163 mg/kg) or 3.5 mg (815 mg/kg) fluoranthene in three installments on days 1, 8 and 15 (1/7, 2/7 and 4/7 of the dose, respectively). Histopathologic examination of the lungs of the mice sacrificed at 24 weeks showed a significant increase in the high-dose group in the total incidence and number/mouse (28/48 or 58%, 1.08 tumors/mouse) of lung tumors compared with vehicle controls (5/55 or 9%, 0.09 tumors/mouse). Tumor response in the low-dose group (10/51 or 20%, 0.24 tumors/mouse) was not statistically significant. While the study presents the first indication of complete carcinogenicity of fluoranthene, this kind of study does not provide data appropriate for quantitative assessment of the carcinogenic potency.

The positive results in the newborn mouse lung adenoma assay (Busby et al., 1984) are supported by reports of positive, though often weak, mutagenic response. Fluoranthene was positive in a test of forward mutation to 8-azaguanine resistance in Salmonella typhimurium strain TM677 (Kaden et al., 1979; Babson et al., 1986). Weak mutagenicity was observed in reverse mutation assays with S. typhimurium strains TA100 (Kinae et al., 1981) and TA98 (Epler et al., 1978) with S-9 metabolic activation. Kinae et al.

(1981), however, obtained negative results with S. typhimurium strains TA98 and TA1537, as well as in the Bacillus subtilis rec assay. Mutagenicity was also indicated in mammalian systems in vitro [in CHO cell HGPRT assays (Li, 1984), in repair-deficient CHO cells (Hoy et al., 1984), in sister chromatid exchange assays with CHO cells (Palitti et al., 1986), all with metabolic activation] and in vivo [with mice bone marrow cells (Palitti et al., 1986)]. Fluoranthene proved negative, however, in a mutagenicity test with a human lymphoblast cell line AHH-1 competent in oxidative xenobiotic metabolism (Crespi and Thilly, 1984) and in a sister chromatid exchange assay using a metabolically competent Chinese hamster liver epithelial cell strain (De Salvia et al., 1988).

These data have led to the classification of fluoranthene as an IARC Group 3 chemical and an EPA group C chemical - possible human carcinogen (U.S. EPA, 1987).

Bioconcentration Factor (BCF)

Pertinent new data concerning the bioconcentration factor for fluoranthene is currently undergoing Agency review. The BCF value of 1150 determined in U.S. EPA (1980) will be used until this review has been completed.

QUANTIFICATION OF EFFECTS

The original ambient water quality criteria for fluoranthene (U.S. EPA, 1980) were derived from a NOEL for mortality in mice treated dermally with fluoranthene over a 12-month period (Hoffmann et al., 1972). Twenty female Swiss Albino mice of Ha/ICR/Mill strain were treated dermally with 50 µl of 1.0% fluoranthene in acetone 3 times weekly for 12 months and observed for 3 additional months. All the mice survived. No skin tumors or other grossly observable lesions were found during autopsy. The exposure level was calculated to be equivalent to 6.12 mg/kg/day, assuming weight for a mouse of 35 g and 100% absorption of the applied fluoranthene, and was taken as a NOEL. With an uncertainty factor of 1000, the human "maximum safe level" was calculated to be 0.006 mg/kg/day or 0.42 mg/day for a 70 kg adult. This figure, after subtracting estimated contributions from diet and air of 0.016 and 0.0001 mg/day, yielded a maximum permissible intake from water of 0.40 mg/day. Using a BCF of 1150, which was calculated from a log K_{oc} of 4.9, the ambient water quality criteria of 42.0 µg/l for daily consumption of 2 l of water and 6.5 g of fish and shellfish and 54 µg/l for fish and shellfish consumption only were derived (U.S. EPA, 1980). Since neither body weight gain nor histopathology nor any other toxicological indices were monitored in the Hoffman et al. (1972) study, any effect that might have occurred other than mortality or grossly observable lesions may have been overlooked.

The new evidence from U.S. EPA (1988) has been selected as the basis for the verified oral RfD (U.S. EPA, 1990). This study reported a LOAEL of 250 mg/kg/day based upon hematologic alterations, increased SGPT levels, and

changes in kidney and liver histopathology, and identified a NOAEL of 125 mg/kg/day. The verified oral RfD of 4.17×10^{-2} mg/kg/day (rounded to 4×10^{-2} mg/kg/day) was derived using an uncertainty factor of 3000: 100 to account for intra and interspecies extrapolation, 10 for the use of subchronic study for RfD derivation and 3 for the lack of reproductive/ developmental and supporting chronic toxicity data.

The unrounded oral RfD value of 4.17×10^{-2} mg/kg/day can be used to calculate ambient water quality criteria. Assuming an average human water consumption of 2 ℓ/day, fish consumption of 6.5 g/day, to kg average adult body weight and using a BCF of 1150 ℓ/kg for fluoranthene, a criterion for ingestion of contaminated water and fish and shellfish of 310 µg/ℓ can be calculated. The criterion for consumption of fish and shellfish alone, applying the same assumptions as above is 390 µg/ℓ.

EXISTING STANDARDS AND CRITERIA

The final RQ for fluoranthene is 100 pounds (U.S. EPA, 1986).

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